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Metronidazole induced neuropathy: clinical & electrophysiological study

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ABSTRACT

Metronidazole, an imidazole derivative is a commonly used drug to treat ameobic liver abscess and many more infections. Side effects include nausea, vomiting, and metallic taste. Uncommonly, peripheral neuropathy on prolonged use has been described which predominantly affect peripheral nerves. In this series seven cases of metronidazole-induced neuropathy from a Tertiary Care Hospital in Northern India are being reported. Patients were all males with mean age of 41.7±6.4 years. The average cumulative dose of metronidazole was 90.7±73.3 grams in this study and mean duration of drug therapy was 50±30 days. Neuropathic symptoms started 2-3 weeks after the initiation of therapy. Neuropathy symptoms consisted of moderate to severe paresthesias in all and glove and stocking distribution of numbness in two cases. Generalized seizures occurred in one case. Electrophysiological study revealed absent sural sensory nerve action potential (SNAPS) in all and diminished sensory nerve conduction velocities (SNCVs) in upper limbs in four and normal in 3 cases. Motor nerve conduction were normal in two and rest five had reduced compound muscle action potential (CMAP) and motor nerve conduction velocity (MNCV) in lower limbs.

INTRODUCTION

Metronidazole is a commonly used nitroimidazole for a variety of indications like ameobiasis, giardiasis, anerobic bacteria, *psedomembranous enterocolitis*, gum infections, Trichomonas and *Helcobacter.Pylori* eradication(1-3). In a typical developing country, cases of both amoebsis and giardiasis are endemic. Hence the use of this drug is extremely common. Metronidazole is taken up by nitrogen dependent uptake mechanisms in susceptible pathogens and acts by inhibiting DNA function by forming free radicals (3). Additionally, it also interferes with functions of intracellular enzymes. The drug has excellent oral absorption and tissue distribution. Nausea, vomiting, metallic taste and disulfiram like reactions are usual side effects. Peripheral neuropathy can be a little known but significant side effect seen on long term metronidazole treatment[3]. However in isolated rare cases central effects (1-2) have also been described. Neurotoxicity described is reversible[1]; therefore early recognition due to physician awareness has been suggested. Drug induced neuropathy is mostly of polyneuropathic type with distal sensory or sensorimotor involvement. Present study was done to know the pattern, dose, duration of metronidazole in producing peripheral neuropathy. In this series, 7 cases of metronidazole induced neuropathy are being described.

MATERIAL & METHODS

There were a total of 7 cases (All males), patients had a diagnosis of ameobic liver abscess and were being treated with metronidazole. All patients were being treated by physicians in the peripheral centers. They were referred to Department of Neurology, for evaluation of neuropathy related complaints within 2-3 weeks of metronidazole administration. Since there was a temporal relationship between drug use and occurrence of symptoms; a provision diagnosis of metronidazole induced neuropathy was made by a qualified neurologist (KSA). Nerve conduction studies were done in all by a qualified technician under the direct supervision of a neurologist (JG), and research associate (VD). Nerve conduction studies (NCV) were done using Cadwell-Seirra Inc., USA Machine, which is a 4-channel Electromyography machine cum Nerve conduction study (EMG/NCV) machine.

RESULTS AND DISCUSSION

The average cumulative dose of metronidazole was 90.7±73.3 grams in this study and mean duration of drug therapy was 45.7±30.3 days. Neuropathic symptoms started 2-3 weeks after the initiation of therapy (details in Table-1).

Table 1. Clinical profiles of patients with metronidazole-induced neuropathy

Number	Age/sex/diagnosis	Dose & duration	Clinical features	Nerve conduction
1.	32/ M/ALA	800 mg TDS x 30 days; cumulative dose= 72 grams	Paresthesia distal upper & lower limbs	MNCS: UL=normal LL=no CMAP recorded from CPN & PTN SNCS= no SNAPS from sural F wave absent from CPN & PTN Normal F wave from median & ulnar
2.	42/ M/ ALA	800 mg TDS x 30 days; cumulative dose= 144 grams	Severe paresthesias both lower limbs 3 weeks after starting metronidazole; bilateral foot drops 4 weeks after	MNCS: UL=normal LL=decreased amplitude of CMAP in CPPT with normal CV SNCS=UL diminished NCV with normal distal latency & amplitude of SNAP LL=no SNAPS from sural nerve F wave normal
3.	40/ M/ ALA	800 mg TDS x 10 days; cumulative dose= 24 grams (oral)	Weakness, numbness in all four limbs & one episode of generalized seizure	Generalized sensory motor neuropathy
4.	53/ M/ ALA	800 mg TDS x 85 days; cumulative dose= 204 grams	'Glove & stocks' distribution of numbness & paresthesia	MNCS: UL=normal LL=decreased amplitude & CV with normal distal latency in CP & PT SNCS=normal F wave absent in UL/LL
5.	45/ M/ ALA	800 mg TDS x 90 days; cumulative dose= 216 grams	Paresthesia in all four limbs, distal	MNCS: normal SNCS UL=decreased SNAP amplitude in median & ulnar nerve LL=no sural SNAPs
6.	42/ M/ ALA	800 mg TDS x 45 days; cumulative dose= 108 grams	Paresthesia and weakness	Motor=normal Sensory Absent SNAPs in all four limbs
7.	38/ M/ ALA	800 mg TDS x 45 days; cumulative dose= 108 grams	Paresthesia of 'glove & stocking' distribution	MNCV: UL/LL=normal distal latency, CMAP amplitude & diminished conduction SNCV: LL/UL=no sural SNAPs, normal latency amplitude & sensory conduction velocity from median & ulner nerve F wave absent from sural nerve & normal in UL

Electrophysiological study revealed absent sural sensory nerve action potential (SNAPS) in all and diminished sensory nerve conduction velocities (SNCVs) in upper limbs in four and normal in 3 cases. Motor nerve conduction was normal in two and rest five had reduced compound muscle action potential (CMAP) and motor nerve conduction velocity (MNCV) in lower limbs.

Metronidazole (1,2) a nitroimdazole has been used extensively for treatment of ameobic liver abscess, anerobic infections, *pseudomemberanous enterocolities*, *H. Pylori* eradication and sexually transmitted infections like Trichomonas etc.

Usual side effects include nausea, vomiting, metallic taste and disulfiram like reactions. Neuropathy is a little known side effect of metronidazole. Metronidazole causes distal symmetrical predominantly sensory peripheral neuropathy which is dose and duration related.

Usual presentation is that of sensory neuropathy rather than motor and is similar to other drugs causing sensory neuropathy[3]. Distal symmetrical burning dysesthesia is the usual presentation and there may be glove and stocking distribution. Both small and large fibers may be affected, latter manifesting as absent or diminished tendon reflexes. Onset of neuropathy may be acute, sab-acute or chronic and signs and symptoms progress if offending agent is not withdrawn. In most cases, recovery can be complete after withdrawal.

Though generally not considered a neurotoxic drug; a few case reports of neurotoxicities of various varieties have been described with the drug (3). Sensi-motor type has been described and is accompanied by axonal degeneration (3-5). A case of autonomic neuropathy in a 15 year old girl has also been described (3). A male patient of 53 years was described who developed insidious onset of length-dependent painful neuropathy on a background of encephalopathy during prolonged treatment with metronidazole for a cumulative dose of 146 g in 88 days[5]. Another case of acute ataxia, disorientation, distal symmetrical sensory and proximal motor neuropathy in a 50 year old man was described (6).

Cumulative neurotoxic doses in literature range from 13.2 grams to 228 grams. Duration has ranged from as short as 11 days to as long as 180 days. A case report of neuropathic pain developing after 3 days of treatment has been described (7).

The suggested mechanisms (8,9) of metronidazole induced neuropathy include: inhibition of neuronal protein synthesis, modulation of gamma-amino butyric acid in the cerebellum, or radical injury to nerve tissue. Though the incidence of neuropathy caused by metronidazole is not known; experience suggests that upto 50% cases may be affected with neuropathy (10). Conventionally, features of axonal sensory neuropathy are seen in most patients. Quantitative sudomotor axon reflex testing has been suggested to be the best diagnostic rest. No reliable test for comparison of these findings (11) is available.

Our cases in present series had been taking metronidazole for ameobic liver abscess and developed neuropathy after a lag period of 2-3 weeks. This period has been similar to earlier described studies. Average cumulative dose too is similar to the one described earlier. Nerve conduction analysis of patients revealed that the patients had mainly sensory neuropathy as described earlier. In a prospective study of metronidazole induced neuropathy, duration of drug therapy (12) has been correlated with occurrence of symptoms.

CONCLUSIONS

It has been suggested that a careful neurological examination and studies of sensory and motor nerve conduction should be performed in patients who complain of paraesthesias, pain, muscle cramps, weakness or other abnormal sensation during treatment with metronidazole. Early recognition, rational use of metronidazole and withdrawal if necessary has been suggested to tackle neuropathy caused by this drug. In the present study, metronidazole has been shown to cause neuropathy in patients taking the drug for hepatic ameobiasis. Metronidazole induced neuropathy is reversible in most cases; however recovery may be partial in some. Physicians should therefore be attentive in noticing the earliest features of metronidazole induced neuropathy and consider stopping the drug.

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